Optimizing Ophthalmic CE ANDA Trials

Clinical Endpoint ANDA Program Optimization
White Paper Series

Wayne A. Bowden, MBA
Ivan Chernetskiy, MD, PhD
Boris Reznik, PhD

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Optimizing CE ANDA trials

Abbreviated new drug application (ANDA) trials involve evaluating drugs that contain the same active ingredient, strength, and dosage form of a drug that has already been approved by the regulatory bodies. Most generic drugs approved through the ANDA process are systemic – the primary mode of delivery is through absorption into the bloodstream, with distribution throughout the body and to the target tissues. Bioequivalence for systemic drugs is normally determined by conducting pharmacokinetic (PK) studies. However some drugs are not intended to be absorbed by the bloodstream. This includes drugs that must be applied directly to the tissue to have the desired effect. These drugs normally require clinical endpoint (CE) studies in order to prove their bioequivalence.

CE studies represent a significant expense for sponsors in both time and money. The process of designing and running CE studies is wrought with choices, decisions, tradeoffs and challenges. Sponsors accustomed to PK trials may encounter an entirely different spectrum of experiences and challenges in CE programs. CE studies can easily last over a year, involve hundreds or even thousands of patients, and cover many clinical sites in multiple countries.

Achieving optimization in CE trials means engaging in careful analysis and decision-making throughout the entire process. Important criteria are: quality, time, industry acceptance, cost, and service level. Although not a prescription, adhering to the old construction proverb of “measure twice, cut once” is a good starting point to begin the journey for a CE ANDA trial optimization.

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Ophthalmology CE ANDA Trials

Drug innovation, development, and marketing in ophthalmology are expanding rapidly in the US as well as around the world. In 2009, sales for these types of drugs totaled over $14 billion and this number is expected to increase considerably. The aging baby boomer population coupled with increasing life expectancies all around the globe will augment this already sizeable market in the years to come.

Ophthalmology is a diverse field, encompassing a broad range of diseases that not only affect distinct areas of the eye itself, but also affect different ethnic, racial, and regional groups. The most widespread disease markets for ophthalmology include glaucoma, dry eye, conjunctivitis, age-related macular degeneration (AMD), and cataracts, among others.

Eye-drops have been used since the age of Cleopatra and are still the most common form of delivery for medication used to treat the various diseases of the eye. Today, however, many different forms of ophthalmic drug delivery are emerging into the market. Delivery can be divided into three general categories:

1. Topical drug delivery, which targets the anterior (outer) section of the eye,
2. Intraocular/subconjunctival delivery, which targets the posterior (inner) section, and
3. Systemic, which is generally administered via tablets or intravenously to treat the disease through the bloodstream.

As discussed earlier, ANDA approval for systemic ophthalmic drugs would likely be conducted via pharmacokinetic (PK) endpoints. However, for topical and certain intraocular delivery drugs, a clinical endpoint (CE) study may be required. So the question becomes:

"When do I need a CE trial?"

Currently, in vivo data (i.e. a clinical trial) is not required for eye-drops if the drug is in the same strength and contains the same active and inactive ingredients as a previously approved ophthalmic solution. This is a boon offered to few other drug-types in the industry. For a generics company, it also offers a unique chance to jump into a market without having to run costly and time consuming clinical trials. However, because generic ophthalmic solutions approved through the waiver are not clinically tested before hitting the market, their adoption is sometimes met with certain skepticism. Problems here could lead to product recalls, redesign, or hesitance by physicians to prescribe the medication, which could potentially hurt profits in the long run. Still, the waiver of in vivo testing for ophthalmic solutions continues to be a potentially lucrative opportunity for the generic drug industry.

The eye-drop as a delivery system for medication has additional limitations. Due to the dense corneal layer of the eye, less than 5% of the typical eye drop solution will penetrate into the anterior chamber – even less into the posterior tissues. Tearing in the eye, especially in response to medication, also contributes to washing out the drug so that less and less is available to be absorbed by the target tissues. To combat this phenomenon, drug innovators have been increasingly using suspensions, emulsions, gels and inserts with the aim of delivering the drug to the target tissues of the eye with greater efficiency. While these technologies do allow superior absorption of the active ingredient into the eye, they are not offered the same waiver as for eye drop solutions. Generics companies seeking ANDA approval for these drugs, or many other drugs in which the major route to the target tissue is not through the bloodstream, will likely need to perform a CE trial.

Our Approach

In this white paper, we concentrate specifically on clinical trials for locally acting drugs that treat diseases of the eye and that require clinical endpoint studies. We identify relevant issues and considerations that arise in these types of studies, having run many ophthalmology trials ourselves. Our method is to approach the subject from a practical standpoint by discussing these issues as they appear in the common phases of a clinical trial: during the design, planning and execution. Our mission is to spark critical thinking in the field - our vision, that the thoughts expressed in this paper will aid the generics industry in achieving successful CE ANDA clinical programs in ophthalmology.

Design

Clinical trial design is the backbone of the study. If the design is flawed, the entire experiment is at risk. During the design, the sponsors determine the power of the study, the endpoints, inclusions and exclusions, the treatment plan and a variety of other factors. Many important considerations for ophthalmic trials emerge during the design phase.

Clinical Endpoints in Ophthalmology CE Trials

Choosing endpoints is especially challenging for ophthalmology clinical trials. The first place the sponsor/CRO may want to look when considering endpoints is in the FDA guidance document for the active ingredient in the indication of interest (indication is important because many drugs serve multiple indications). The guidance contains recommendations set forth by the FDA including, at times, the appropriate endpoint for the study. After analyzing the guidance, the sponsor or CRO should review the summary basis for approval (SBA) for the RLD. As the name suggests, this document contains a summary of the NDA for the drug. The endpoints measured for the RLD will be detailed in the SBA, along with other helpful information such as how many patients were tested, what variability, and what order of significance was obtained by the study.

Unfortunately, for many drugs the FDA guidance and SBAs are either not available or do not contain the required information needed by the sponsor to determine the endpoints. The study designers then have to determine the endpoint themselves, considering multiple regulatory and clinical factors. In our introductory white paper, 10-10, and in our white paper, 10-11 (Patient Numbers Required in CE ANDA trials), we point out some important endpoint considerations, such as endpoint expression (i.e. the endpoint is measured as a mean change from baseline or as the proportion of patients who meet some particular level of change from baseline).

Every endpoint decision has common elements, but because every endpoint is different, each decision has its own set of considerations. We will touch upon a few of these considerations which are unique to ophthalmology CE trials. Some of the endpoints used to measure therapeutic equivalence in common ophthalmology clinical trials are given in Figure 1.

Visual function endpoints are used in studies involving diseases that can cause blindness if left untreated. This includes glaucoma, cataracts, AMD (both wet and dry), macular edema, and diabetic retinopathy. There are multiple parameters of visual function: visual acuity, visual fields, contrast sensitivity, dark adaptation and color vision.

	Indication	Visual Function Endpoints				OCT	Other Endpoints
		ETDRS	Visual Field	Color Vision	Contrast Vision		
Back of the Eye	Open Angle Glaucoma	X	X	X			IOP; VFQ[4]-25
	Neovascular AMD[1]	X				X	VFQ-25
	Geographic Atrophy	X	X				Reading Speed
	Diabetic Retinopathy	X		X	X	X	VFQ-25; Microaneurism Counts
	Uveitis	X					Vitreous haze
Surface of the Eye	Dry Eye		Schirmer's Test; TBUT[2], OSDI[3]				
	Allergic Conjunctivitis	X	Ocular Itching; Conjunctival Redness				
	Bacterial Conjunctivitis		Microbial eradication				

Figure 1 Table 1: Endpoints used in common clinical trials for ophthalmology.
[1]Age-Related Macular Degeneration [2]Tear Breakup Time [3]Ocular surface disease index
[4]Visual Function Questionnaire

Visual acuity and field are probably the most frequently used endpoints. The most widely accepted endpoint to assess visual acuity is the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart (Figure 2). This chart replaced the well-recognized Snellen Eye Chart in clinical trials because it was more standardized, and offered a logarithmic scale of lettering size reduction from line to line. By far, the greatest criticism of the ETDRS endpoint has been that the commonly accepted 15-letter (3-line) change required for significance is quite difficult to achieve, even when other endpoints indicate a clear advantage of the investigational drug over the placebo. In fact, experts have suggested that with some slowly progressing diseases, the 3-line change is just plain unachievable, or at the very least prohibitive because of the time and patient numbers required.

In the case where endpoints are difficult to achieve, the trial should consider using two surrogate endpoints instead. Surrogate endpoints, though not substantially enough on their own, are widely accepted by the FDA in concert with other endpoints to effectively demonstrate significance. An example would be a 2-line change on the ETDRS, along with a microaneurism count.

Figure 2: ETDRS Chart for examining visual acuity

Visual field endpoints are useful to study the progression of diseases like diabetic retinopathy and glaucoma (though the primary endpoint for glaucoma is measurement of IOP). Kinetic perimetry, static perimetry, and microperimetry are all functional diagnostic tests used to assess the degree of visual field changes over time, none of which are standard for any type of disease. Many studies will include a color vision, or dark adaptation endpoint to assess different aspects of the disease progression. These choices may depend on what sort of clinical outcome is expected from the investigational material (i.e. what particular symptom is the drug intended to treat?).

Tear production endpoints are important in the diagnosis and monitoring of diseases such as dry eye. Dry eye is a disorder of the eye characterized by a dysfunction in tear production and is often accompanied by moderate inflammation of the conjunctiva. The disorder is currently treated by the brand drug Restasis® (Allergan), a cyclosporine emulsion. The clinical endpoints recommended by the FDA for drugs treating dry eye include Tear breakup time (TBUT) and the Schirmer's test, which assess or measure tear production, as well as corneal staining, which can assess the degree of corneal damage associated with chronic dryness.

Questionnaires are also widely used for endpoints. The subjectivity inherent in patient self-assessments has been well documented for many indications, and the same is seen for ophthalmic trials. The severity of symptoms for diseases of the eye may vary greatly from patient to patient and may not correlate with the clinical signs. For instance, it is not uncommon for a patient with severe signs of dry eye to experience very little discomfort while a patient with moderate signs experiences significant pain and discomfort. Due to this variability, any patient assessment endpoint must be thoughtfully selected and properly controlled to enhance the significance of the study and increase the chances for success.

Finally, there is increasing support for the use of sophisticated technologies in the diagnosis and monitoring of diseases of the eye, such as Fourier domain optical coherence tomography (OCT). OCT is able to provide in-depth and detailed models of the retina, and has the potential to be able not only to diagnose but also to predict occurrence of diseases of the retina such as AMD and diabetic retinopathy. While emerging technologies such as OCT, and other technologies like the retinal camera, will become the endpoints of the future, many of them have not yet been positively shown to correlate with clinical significance (OCT is only currently used as a secondary endpoint). Sponsors should weigh alternatives before including these tests in trials because it may be unlikely that the results will contribute significantly to the primary endpoints of the study.

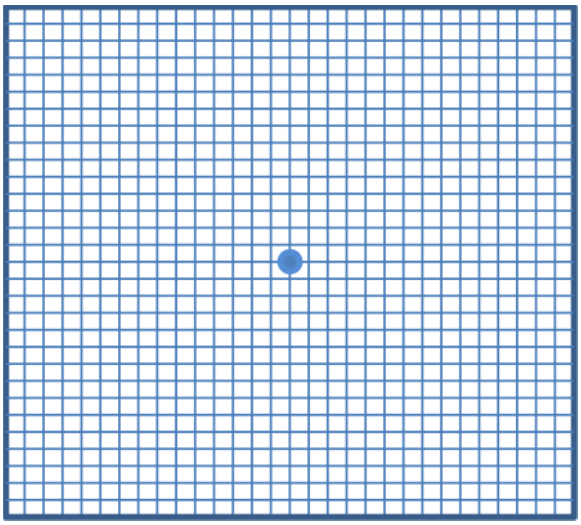

Figure 4: Amsler Grid for diagnosing macular degeneration

Determining the Subject Numbers

As with any clinical trial, one of the primary challenges is deciding how many patients to recruit. On the one hand, cost incentives encourage those conducting the study to enroll the least number of patients. On the other hand, there must be enough patients to showa $p<0.05$; at the end of the day, one would rather see the study be overpowered (too many patients) than underpowered (not enough). Sponsors must realize that the required limit for equivalence in the US is set to 20% for ANDA trials. In our previous white paper, 10-11, we developed an integrated decision map to help the industry tackle the double-edged sword, so to speak, of finding the optimal patient number in CE ANDA trials. Please refer to that paper for a more detailed discussion about patient dropout rates, statistical considerations, and endpoint expression.

One not-so-obvious complexity involved in choosing an appropriate patient sample size is nearly unique to ophthalmic clinical trial: each patient has two eyes, and most diseases are bilateral. If the statistical analysis suggests that the study will require 100 eyes, should the sponsor plan to enroll 100 subjects, or just 50 subjects and use both eyes? In fact, there is no one answer. However, most designers will assume only one eye is tested (all left or all right). This increases the probability that the sample size is sufficient to yield valid results (noncompliance by one patient does not compromise two “study” eyes), and ensures that there is less bias in the study design (two eyes from the same patient are more likely to behave in the same fashion than two eyes from different patients).

For ophthalmic clinical trials, the disease indication plays an important role in budgeting for screen failures. An excellent illustration of this point is in dry eye, where screening failures are quite common. Dry eye symptoms may be a temporary result of a procedure, such as LASIK, or the manifestation of a completely separate disease, such as Sjogren's syndrome or rheumatoid arthritis. Many patients who are initially thought to have the disorder actually do not have it. At the very best, unanticipated screen failures prolong the enrollment process; at worst, they cut into the patient population needed for the primary endpoints. More than half of clinical trial delays are the result of inadequate recruitment. In order to accurately estimate screening and enrollment numbers from the start, the designers should think critically about how that indication will influence the numbers needed for the study.

FDA Interactions

There is currently little guidance from the FDA for ophthalmic drugs. For many indications, there is no standard endpoint recommendation. Many new technologies are making their way into ophthalmology diagnostics and may be used as endpoints in the future. In addition, FDA regulations regarding approvals of ophthalmic drugs can be at times vague and unpredictable, hindering companies' ability to get the approvals they need. Thus, more communication with the OGD officials is merited. CROs are also adept at navigating through the regulatory mire, as these organizations have experience working with the OGD. Choosing a CRO experienced in CE ANDA trials is also important, as the OGD treats PK trials differently than CE trials. Thorough communication with the FDA and/or partnering with an experienced CRO can facilitate the design process and result in a more sound study design.

Planning and Feasibility Considerations

During the planning and feasibility phase, sponsors and CROs select where the study is to be conducted and who will be conducting it. The planning phase is not an independent decision making process. On the one hand, the process draws from decisions and assumptions made in the design phase. On the other hand, it is based upon knowledge and experience the sponsor and CRO possess in the pertinent areas of the trial. Important considerations emerge, particularly when deciding on sites, PIs, logistics, vendors, labs, and many other elements. Attention to these elements is key in optimizing the trial's performance and outcome. Here we will present some issues specifically affecting ophthalmology trials.

Geography

One of the primary objectives in site/country selection is determining how to get the greatest number of Enrolled/ ITT/PP subjects in the shortest amount of time. To do so, one must choose locations that optimize both the patient and the physician (PI) elements. The US, Europe, and China run the majority of trials in ophthalmology registered with clinicaltrials.org. For the sponsor, running trials in high volume areas means that the sites there may have the benefit of experience in ophthalmic clinical trials. By chance, the site may have run a trial recently with the particular disease of interest. PI experience with that particular indication could potentially help to reduce variability in measurement. Experience in running a trial is also a factor that greatly reduces waiting time such as for regulatory documents, approvals, and signatures.

However, choosing a high volume site can also be problematic. Competing for the same patient and/or PI population as another trial can potentially hew enrollment rates, abolishing any advantages that may have been expected. Therefore, when questioning a site for selection, the question of, "have you ever run this trial?" should always be followed by, "are you running this trial right now or planning to run it in the near future?"

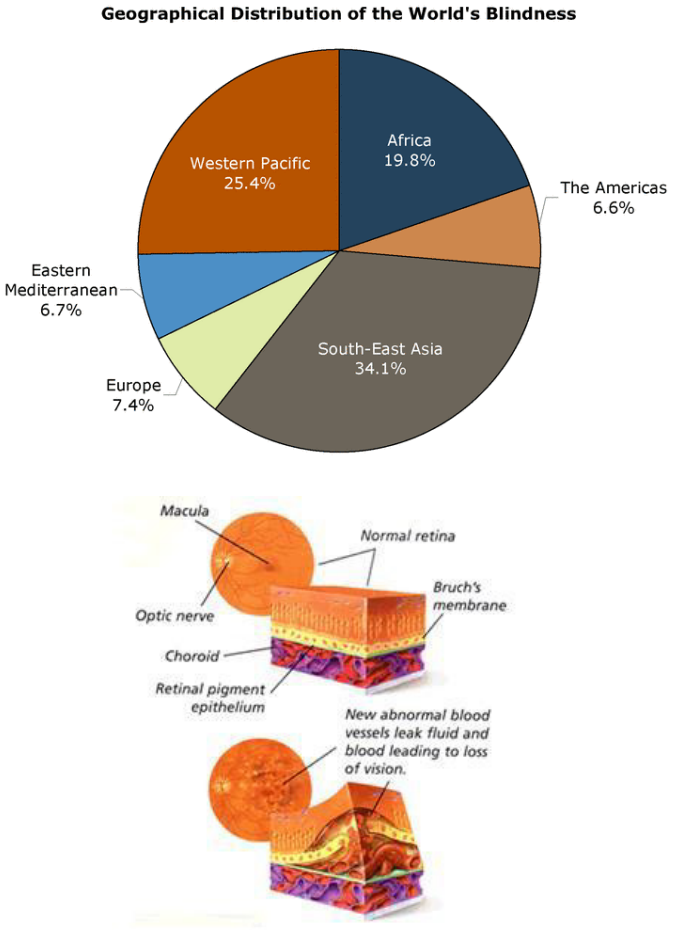

Figure 5: Neova cular (wet) age related macular degeneration.

Looking elsewhere may also have its advantages. Sites in the US and Europe may not have the proper demographic mix for the disease indication of interest. Foreign sites may harbor untapped populations, more densely populated sites, or populations with more advanced stages of disease. Eastern Europe, South America and Central America have emerged as promising areas for conducting clinical trials.

Countries such as Russia, Ukraine and Mexico harbor unique advantages. First, relatively few ophthalmic trials are conducted there, so competition is minimal. Second, these countries have very large patient flows through few major central hospital systems. Such attributes may compel the sponsor, for good reason, to seek patients outside the typical sphere of operations.

Importantly, when considering foreign site selection, the sponsor should also consider conducting a portion of the trial in the US to satisfy recent reservations, which have been expressed by the OGD. Selection and partnering with a global CRO is a compelling option for sponsors who would like to have a wide selection and keep the authorities satisfied at the same time.

Demographics

While most diseases of the eye are age-related, nearly no two diseases affect the same type of patient. For example in the US, the leading causes of visual impairment for whites are, overwhelmingly, AMD and cataracts. For blacks however, it is cataracts and glaucoma (and diabetic retinopathy) – their risk for AMD is 10 fold less than it is for whites. Hispanics, on the other hand, suffer much less than both of those groups from cataracts but have higher glaucoma incidence than both. Similar patterns can be seen when comparing men and women, social status, and a myriad of other determinants. Study demographics are thus of critical importance. Taking the time to analyze each potential site based on this factor will cut costs and save time by enhancing the enrollment process. The sponsor/CRO may find that a site previously thought to be secondary due to size is actually primary because of the patient demographic (and thus incidence of the specific disease) mix. Of course, working globally offers a greater choice of populations.

Logistics

Logistics refers to the supply and management of material and personnel during an operation. Logistics is a major factor of the execution phase that must be considered in the planning process. As discussed earlier, a major challenge in the ophthalmology clinical trial is in reducing measurement variability. During the planning process, the sponsor or CRO must make decisions regarding how to increase the power of the study using imaginative logistics techniques. For example, to reduce variability as much as possible, the sponsor or CRO might decide that it is feasible to utilize medical device distribution for the critical measurement devices from site to site, so that each patient is measured with the same array of devices. This may not be feasible for devices measuring a secondary endpoint, as this sort of logistics plan can become costly. However, for smaller trials, or trials where sites are distributed close together, a logistics plan for distribution of personnel or devices could be merited. Additionally, such logistics plans give the sponsor/CRO a greater amount of control over the management of critical supplies, which they might not have if they left such management up to the sites.

"Intellectuals solve problems, geniuses prevent them."
- Albert Einstein

Optimizing CE Ophthalmology Trial Execution

Proper execution of complex clinical trials is difficult, but achievable. Ophthalmic clinical endpoint studies are especially difficult because endpoint measurements are subject to large amounts of variability. Differences in how individual patients apply medications further increase this variability. High quality training of physician and patients coupled with hands-on site management can help to reduce these sources of variation.

Rater and Patient Training

Training during the execution of the clinical trial has been shown to reduce variability in measurements and smooth operations from the outset. In a future white paper, we will explore ways to maximize the benefits from the training experience in greater detail. In essence, both investigators and patients need to be trained effectively with study-specific materials. While training is an important element in any trial, we will discuss this important factor as it relates to CE ophthalmology trials.

Ophthalmologists generally run a similar battery of tests to treat and manage ophthalmic diseases, but these objective measurements are far from reproducible from doctor to doctor. Even the same doctor may not be able to reproduce the same results on a day-to-day basis. If measurement methods are not standardized and well communicated by the sponsor/CRO at the beginning of and during the trial, one can expect that these inter and intra-rater differences will manifest at the conclusion of the study with increased variability of the results. For example, a variety of techniques exist for measuring intraocular pressure in glaucoma trials. Each technique is different and if not uniformly performed, could produce different results. Even using the same technique, performing the test on different tonometers (there are several kinds) with different calibrations may yield different results. Failing to train the investigators to use a single technique or to standardize the tonometers being used throughout the sites could create enough variance to diminish the therapeutic evidence of the drug.

Physicians should always be trained with the specific clinical endpoints measurements in mind. Iterative training, in which the physician's own training results are used as a basis for further training, is an especially useful technique. Furthermore, the training should address those unique variables that could affect the trial, which we have discussed: demographics, inclusion and exclusion criteria, etc. For instance, physicians could be reminded during their training that the symptoms of disorders such as dry eye are highly dependent on the time of day (morning versus evening) and environment (arid versus humid). Or, that IOP varies from night to day due to fluctuations in blood pressure. The training could then focus on ensuring that measurements during the course of the study are conducted at the same time of day and in a controlled environment.

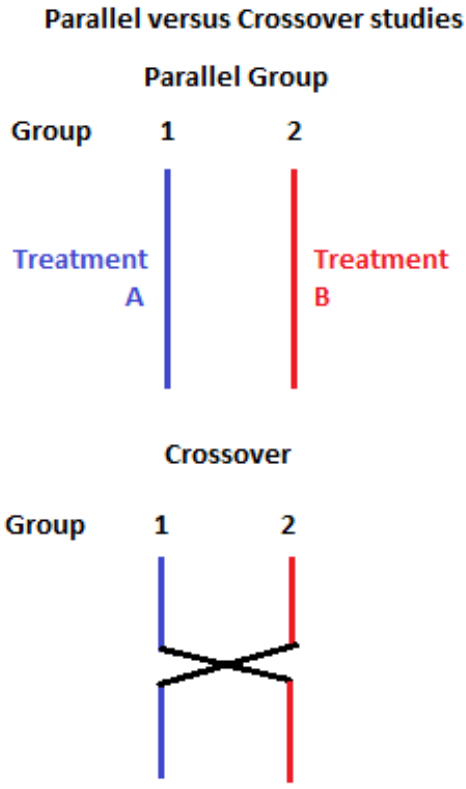

Figure 6: In a parallel study, all patients in group 1 receive treatment A, and group 2 gets treatment B. In crossover, patients receive either treatment A or B first for a period of time, washout, then receive the other treatment for the remainder of the study.

Training for patients is equally important as it is for physicians and especially for topical medications because the amount of drug used may vary greatly from patient to patient. Many sponsors/CROs may simply instruct patients to follow a particular dosing regimen. While instruction is helpful, interactive training is the goal. This may be accomplished by having the patient actually apply the placebo in the clinic, so that the physician can give feedback based upon precise observations and require the patient to repeat the procedure to assure uniformity in application. Ophthalmology trials with poor training commonly produce undesired results. For example, one patient may use one drop of solution and wipe the excess solution from the eye after application, while the next patient may use two drops and leave the solution in. In allergic conjunctivitis, patients may self medicate in response to different allergens and environmental factors. One can see that the dosage for one untrained patient may then be very different from the next.

Most ophthalmology studies are parallel group and not crossovers, so standardization of the treatment regimen across all patients is extremely important; otherwise, inter-patient differences between groups could compromise the study. The protocol should include specifics as to when, where, and how to apply the drug. Again, interactive training of both physicians and patients is warranted.

Patient diaries are another common element in ophthalmology trials. Diaries are an excellent source of assessment from the patient's perspective and can provide very meaningful results as far as safety and efficacy. However, noncompliance and poor data quality is a major concern for diaries. One solution may be to use electronic diaries, which have been shown to increase compliance with standardized data entry. Whichever format is used for the diary, however, the patient must be trained as to how data is entered into the diary and physicians should be routinely monitoring diary entry throughout treatment to correct any issues that may arise.

Clinical Site Management and Follow Up

Good site management is essential, in part because many ophthalmic endpoints are subjective, and thus variable. For example, a patient's performance on the ETDRS can be affected by a variety of factors including pupil size, literacy, and ambient lighting. As discussed before, even measurements of objective tests such as IOP in glaucoma are a function of the machine's calibration and/or the technique used. The same goes for machines measuring perimetry for diabetic retinopathy. Some machines may need to be recalibrated during the study. Other endpoint considerations may need to be reiterated as well. The use of monitors highly experienced in ophthalmology trials and knowledgeable in the aspects of the particular trial and protocol is a must.

Consistent and constant communication with the sites during the execution of the trial can help to ensure that training did not go to waste. Applying all the techniques above will help to keep the data quality high and data variability low. At the same time, follow up with patients can ensure increased retention rates (patients are more likely to comply when communication is open) and even help to reduce the variability in topical dosing as discussed above. For example, by weighing the amount of remaining medication amidst the study the physician can assess how much medication an individual patient is using. If the patient is using too much or too little, this will give the physician a chance to advise the patient accordingly.

"Excellence in not an act, but a habit."

- Aristotle

Continuous Improvement

There should always be time allocated at the end of a study to go back and assess how well the study was performed. Likely, there will be more opportunities to run clinical trials in the field of ophthalmology in the years to come. Thus, learning from the experience is essential to future success. Simple, anecdotal review is a poor substitute for a formal and diligent Continuous Improvement Process (CIP). The process is based upon development of specific criteria and measurements prior to conducting the trial. Analysis of the achieved results by measurement against criteria benchmarks is a powerful way to make the necessary improvements for the next time around. Every trial is different, but experience and application of the CIP are the paths to a higher degree of optimization in the future. We will dedicate one of future white papers to the CIP to help the sponsor make this improvement process a standard element in the clinical trial process.

Figure 7: Considerations during different phases of the Ophthalmology CE trial.

Conclusion

Here, we have discussed some of the factors that come into play when deciding when and where and how to run a CE trial in ophthalmology. Furthermore, we touched briefly upon a few of the common indications and endpoints for these types of trials, and the elements which must be considered in order to optimize the trial. Clearly, there are additional challenges that merit consideration, and more than can be discussed in the scope of a single white paper. Though we have only just begun to scratch the surface, in future papers we will delve deeply into some specific areas of topical ophthalmic drug CE clinical trials, with an emphasis on the practical aspects of answering the most important question:

"How can I ensure the highest probability of success of my Ophthalmic Drug's CE program at the lowest cost and in the shortest time?"

"Although personally I am quite content with existing explosives, I feel we must not stand in the path of improvement."
- Winston Churchill

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bioRASI White Paper No. 10-11. Patient numbers required in clinical endpoint ANDA trials.

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Biorasi Global Headquarters
Address: 19495 Biscayne Blvd. Suite 900
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Phone: 786.888.2129
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